

PATENT COOPERATION TREATY

(scad. 02.02.06)

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing:

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/001818

International filing date (day/month/year)
22.02.2005

Priority date (day/month/year)
01.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/4545, A61P25/28

Applicant
MEDESTEA INTERNAZIONALE S.R.L.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001818

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001818

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-8

because:

☒ the said international application, or the said claims Nos. 6-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/001818

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-8
	No: Claims	9,10
Inventive step (IS)	Yes: Claims	
	No: Claims	1-8
Industrial applicability (IA)	Yes: Claims	1-5,9-10
	No: Claims	6-8

2. Citations and explanations

see separate sheet

1. Section III

Claims 6-8 are directed to a method of treatment of the human/animal body by therapy. Such subject-matter is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, and therefore no opinion shall be formulated with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). However an opinion shall be formulated with respect to novelty and inventive step based on the alleged effects of the compounds/compositions.

2. Section V

2.1 Cited Documents

The following documents (D) are referred to in this Opinion; the numbering will be adhered to in the rest of the procedure:

- D1: US-A-5 981 548 (PAOLINI ET AL) 9 November 1999
- D2: EP-A-1 132 085 (DAIICHI RADIOISOTOPE LABORATORIES, LTD;
YAMAGATA PUBLIC CORPORATION FO) 12 September 2001
- D3: GUAN ZHI-ZHONG ET AL: "Loss of nicotinic receptors induced by beta-amyloid peptides in PC12 cells: Possible mechanism involving lipid peroxidation." JOURNAL OF NEUROSCIENCE RESEARCH, vol. 71, no. 3, 2003, pages 397-406, XP009050302
- D4: SÓTONYI PÉTER ET AL: "Comparative study on cardiotoxic effect of Tinuvin 770: a light stabilizer of medical plastics in rat model." TOXICOLOGICAL SCIENCES, vol. 77, no. 2, February 2004, pages 368-374, XP002334830
- D5: DATABASE PUBMED [Online] Department of Health and Human Services; August 2002 (2002-08), LEVIN ED, REZVANI AH: "Nicotinic Treatment for Cognitive Disorders" XP002334833 Database accession no. 12769614
- D6: HERNANDEZ C M ET AL: "Regional and sub-type specific upregulation of cholinergic receptors with nicotine, mecamylamine and cotinine" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27(2), 2001, page 2133, XP001206875 & 31ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; SAN DIEGO, US; NOVEMBER 10-15, 2001
- D7: FRANCIS MICHAEL M ET AL: "Sensitivity to voltage-independent inhibition

determined by pore-lining region of the acetylcholine receptor" BIOPHYSICAL JOURNAL, vol. 74(5), 1998, pages 2306-17, XP002334831

Unless otherwise indicated reference is hereafter made to the passages cited in the Search Report

2.2 The prior art

US 5 981 548 A: The document discloses that the compounds of the present claims are able to capture superoxide radicals and provide therefore anti-radical protection. They are said to be lipophilic agents, as such they are able to pass biological membranes. The skilled person knows that the blood-brain barrier is one such barrier.

EP 1 132 085 A: The document discloses that agents able to scavenge free radicals, and oxygen radicals in particular, can be used for the treatment of a number of diseases, among which are neurodegenerative diseases. The document further claims compounds that closely resemble those of the present claims.

XP009050302: The document establishes a link between lipid peroxidation and the loss of nAChRs associated with the pathogenesis of Alzheimer's disease.

XP002334830: The document discloses that Tinuvin 770, a compound falling under the scope of the present claims, binds to the $\alpha_4\beta_2$ acetylcholine receptors with high affinity in the central nervous system. It further discloses that it is a more potent blocker of nAChRs than mecamylamine.

XP002334833: The document discloses that the $\alpha_4\beta_2$ acetylcholine receptors are involved in working memory and that nicotinic medication may provide effective treatment in Alzheimer's disease.

XP001206875: The document discloses the efficacy of mecamylamine in increasing high affinity AChRs in the cerebral cortex. It also establishes a link to the treatment of Alzheimer's disease.

XP002334831: The document analyses the activity of three analogs of Tinuvin 770 (BTMS) falling under the scope of the present claims. It comes to the conclusion that, among other factors, also the length of the compound has an effect on binding to nAChRs, the perfect length being that of BTMS.

2.3 Art 33(2) PCT (Novelty)

The subject-matter of claims 9 and 10 of the present application does not meet the requirements of Article 33(2) PCT.

Document D1 discloses the first medical use of the presently claimed compounds.

2.4 Art 33(3) PCT (Inventive step)

The subject-matter of claims 1-8 of the present application does not meet the requirements of Article 33(3) PCT.

The present general formula includes two families of compounds, those where R6=H and those where R6 is O or OH. For the two families of compounds two different approaches to the evaluation of the presence of an inventive step must be adopted, given what is known in the prior art. The attention of the applicant is drawn to the fact that in the evaluation of inventiveness what matters is if the prior art suggests the use of the given compounds for the treatment of the given diseases, independently of the mechanism by which such treatment occurs.

2.4a For compounds where R6 is O or OH their use in the treatment of neurodegenerative diseases is suggested by the combination of the teachings of document D1 on the one side and documents D2 and D3 on the other, which establish a connection between compounds capable of trapping free radicals and the development/treatment of Alzheimer's disease (*vide supra*). It is observed that document D1 itself describes the ability of the compounds to pass lipophilic barriers, and therefore there is no surprising effect when they are able to pass one of these membranes, the blood-brain barrier (cf present description, p. 5, § 3).

2.4b For the compounds where R6 is H their use in the treatment of neurodegenerative diseases is suggested by the combination of the teachings of documents D4-D7. These documents suggest the medical use of at least one such compound, namely Tinuvin 770, as a consequence of its action on AchRs (although this mechanism has nothing to do with the trapping of free radicals). Further to this, document D7 teaches that the useful compounds must have a precise length, around C10. The present claims claim any length between C1 and C30, and there is therefore good reason to doubt that the problem of finding new compounds able to treat neurodegenerative disorders is solved over the whole scope of the claims.

2.5 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 6-8 are industrially applicable since their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

2. Section VI

Other cited documents (Rule 70.10 PCT)

Patent number	Filing date	Priority date	Publication date
WO 2005/032479	30.09.2004	01.10.2003	14.04.2005
US 2005/065182	23.09.2003	-	24.03.2005

WO 2005/032479: The document discloses the use of 2,2,6,6-tetramethylpiperidin-4-yl heptanoate for the treatment of neurodegenerative diseases.

US 2005/065182: The document discloses the use in medicine of 2,2,6,6-tetramethylpiperidin-4-yl sebacate and succinate.